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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/308,829	07/14/99	SCHLIEVERT	P	600.347USWO

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EXAMINER	
HINES, J	
ART UNIT	**PAPER NUMBER**
1641	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/308,829	Schlievert et al.
Examiner	**Group Art Unit**
Ja-Na Hines	1641

☒ Responsive to communication(s) filed on *Jul 14, 1999* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-16* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-16* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Specification

1. The use of the trademark ELISA ™ and other diagnostics and reagents have been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

2. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Streptococcal pyrogenic exotoxin type C (SPE-C), does not reasonably provide enablement for altering the amino acid sequence by any insertion, deletion or substitution of one more amino acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims and specification recite mutant to mean any SPE-C that is not completely identical to the wild-type SPE-C, and that a mutant can be obtained by deletion, substitution or insertion of one or more amino acids, however that specification only provides guidance to specific amino acids and does not teach all amino acids changes that may or may not be changed without causing a detrimental effect to the peptidase to be produced. The claims broadly teach at least one amino acid deletion, substitution or insertion, therefore any amino acid is being claimed, and no specific location for where the deletion, substitution or insertion or any combination thereof is recited, if all the amino acids are deleted or substituted or inserted the resulting mutant SPE-C could result in a mutant toxin not taught and enabled by the specification.

The specification does not provide substantive evidence that the claimed vaccines which broadly teach the deletion, substitution or insertion of any amino acid is being claimed is capable of inducing protective immunity. This demonstration is required for the skilled artisan to be able to use the claimed vaccines for their intended purpose of preventing Streptococcus infections.

Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict if protective immunity has been induced by any mutant of SPE-C.

Thomas E. Creighton, in his book, "Proteins: Structures and Molecular Properties, 1984",(pages 314-315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes:

1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge;

2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a Proline residue, which must distort the alpha-helix;

3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book "Protein structure: A Practical Approach, 1989; pages 184-186" teaches that present day site directed mutagenesis of a gene allows any amino acid in a protein sequence to be changed to any other, as well as introducing deletions and insertions. The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in "Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph) adds support to Thomas E. Creighton, by teaching that

results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

The substitution of any amino acid in any location within the mutant SPE-C would not predictably result in a stable molecule. The specification only teaches the use of specific amino acids in specific locations which result in stable variations. The specification does not provide guidance on how any amino acid can be deleted, substituted or inserted for the production a stable bacterial SPE-C nor does the specification provide guidance on how any location can be used to produce a stable protein. No working examples are shown containing the missing information. Without such information, one of skill in the art could not predict which deletions, substitutions or insertions or any combination thereof would result in the desired stable, active protein. Accordingly, one of skill in the art would be required to perform undue experimentation to use any amino acid at any location to produce a stable SPE-C toxin. Therefore, one skilled in the art could not make and/or use the invention without undue experimentation.

4. Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Acronyms like SPE-C must be spelled out when used for the first time in a chain of claims.

5. The recitation of "substantially nonlethal compared with a protein substantially corresponding to the wild type SPE-C toxin" in claim 1 is vague. The term substantially is not defined by the claims or specification such that one skilled in the art would be able to ascertain what level "substantially" would represent. Further, it is unclear how to determine how substantial nonlethal and the correspondence need to be with respect to the wild type toxin.

6. Claims 3-9 are unclear. The specification, in example 6 and claims 3-9 refer to the mutant SPE-C having an amino acid change at amino acid asparagine 38, however, the description at page 11, line 24 and Table 2 cite the substitution at asparagine 37. Applicant is required to explain the discrepancy.

7. Claim 10 recites substantially enhance endotoxin shock, therefore has the same problems as Claim 1, see above.

8. Claim 16 is unclear as to whether the method for reducing symptoms associated with toxic shock reduces all the symptoms associated with the disease or only one or a few. The claim is also indefinite in its recitation of reduced. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree of relativity, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear how to define what levels of reduced symptoms and what level of reduction need to be achieved.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1 and 13-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Goshorn et al. Goshorn et al., teaches the nucleotide sequence of Streptococcal Pyrogenic Exotoxin type C and found that the SPE-C had the greatest sequence homology with SPE-A (abstract). SPE-C is a member of a family of biologically and biochemically related toxins produced by *Streptococcus pyogenes* and *Staphylococcus aureus* (page 2518). The toxins occur in three serologically distinct forms, A, B and C and have been associated with streptococcal toxic shock-like diseases (page 2518). The authors have also previously reported the cloning of the gene for SPE-C where the gene was localized, DNA fragments were ligated to bacteriophages, transformed in *E. coli* and recombinant phages were selected (page 2518). Deletion subclones were obtained using exonuclease activity and further suggest using site-directed mutagenesis to analyze the toxin (page 2518). The SPE-C amino acid sequence was found to be highly related to SPE-A sequences and found to have a high degree of similarity by allowing conservative amino acids changes (page 2519, Table 1 and Figure 2). The amino acid alignments reveal some clusters of conservation particularly in the carboxyl halves of the proteins, however the regions

may represent biologically important sites necessary for the structural integrity of the proteins (page 2519).

Therefore, Goshorn et al., teaches a mutant SPE-C toxin with at least one amino acid change as compared to the wild-type SPE-C.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-10 and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goshorn et al., in view of Kline et al. Goshorn et al., has been discussed above, however, Goshorn does not teach specific amino acid changes. Kline et al., teaches the analysis of the superantigen activity of mutant and allelic forms of SPE-A. Bacterial superantigens associated with food poisoning and or associated with Toxic Shock Syndrome 1 and 2 or the streptococcal toxins SPE-A, SPE-B and SPE-C are known for there ability to overstimulate the host immune system (page 866). The authors generated 20 mutant forms of SPE-A and the mutant toxins were analyzed for mitogenic stimulations of human peripheral blood formulations and the residues necessary for each function was identified (abstract). Mutational analysis of SPE-A was done in order to define the regions of the toxin important for this activity, hence 20 mutants forms were

analyzed for their mitogenic activity and their affinity for class II MHC molecules (page 861-862). Also, the important of a potential disulfide loop in the ability of the toxin to stimulate immunocytes and bind to class II MHC molecules was evaluated (page 832). The Materials and Methods section teaches the construction of a transformed host cell, DNA sequences encoding SPE-A, generations of point mutations in SPE-A, mitogenicity assays and determination of the structure of SPE-A. The positions of the 20 additional amino acids substitutions are shown in Figure 2, 16 of the residues were chosen based on the fact that these residues are known to be important for activity of the closely related bacterial superantigen SPE-B (page 863). An example substitution was at position 12 to an alanine residue (page 863). Figure 3 shows the mitogenic activities of the SPE-A mutants and Figure 4 shows the mitogenic activities at mutant and allelic forms of SPE-C as compared to recombinant SPE-A.

Therefore, it would have been obvious at the time of applicants invention to have used the mutant SPE-C as taught by Goshorn et al., in the method of Kline et al., because Goshorn et al., teaches that SPE-C has the greatest sequence homology with SPE-A wherein the amino acid alignments reveal some clusters of conservation and the regions may represent biologically important sites necessary for the structural integrity of the proteins and SPE-C is a member of a family of biologically and biochemically related toxins produced by *Streptococcus*.

11. Claims 11-12 and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goshorn et al., in view of Leung et al. Goshorn et al., has been discussed above, however,

Goshorn does not teach the use of toxins comprised within a vaccine. Leung et al., teaches that streptococcal exotoxins or homologous exotoxins may be involved in the pathogenesis of acute Kawasaki syndrome and it has been found that Kawasaki and its associated antigens are produced by bacteria which also produce the toxic shock syndrome toxin (TSST-1) (col. 2 lines 60-68). In some of the cultures obtained from untreated Kawasaki syndrome patients, streptococcal pyrogenic exotoxins, SPE-B and C were also found (col. 3 lines 57-67). The invention the use of anti-toxic shock syndrome -1, anti-SPE-B or anti-SPE-C agents which can be administered to an infected subject (col. 7 lines 57-61). Modulation of the immune response can take several forms, such as administration of a mutated TSST-1 or mutated, non-pathogenic TSST-1 S. Aureus in a manner that elicits a protective immune response (col. 8 lines 4-10). The mutated forms refers to materials where some fundamental change has been made such as an addition, substitution or deletion of amino acids has occurred (col. 8 lines 29-36). Any of the materials can be used as vaccines, wherein the vaccines can include other materials such as an adjuvant (col. 87 lines 36-39).

Accordingly, it would have been obvious at the time of applicants invention to have used vaccines or pharmaceutical compositions comprising a mutated toxin as taught by Leung et al., wherein the toxin is SPE-C as taught by Goshorn et al., because Leung et al., teaches that pharmaceutical compositions comprising mutant toxins is well known in the art and can modulate the immune response to provide protection against the bacterial pathogen.

Prior Art

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Hovde et al., teaches the investigational role of the disulfide bond in the activity and structure of Staphylococcal enterotoxin C1. Goshorn et al., (Mol. Gen. Genet.) Teaches the cloning and characterization of the SPE-C gene for *Streptococcus pyogenes*. Norrby-Teglund et al., teach the detection and nucleotide sequence analysis of the SPE-C gene in Group A Streptococcal isolates.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is (703) 305-0487. The examiner can normally be reached on Monday through Thursday from 6:30am to 4:00pm . The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Ja-Na Hines

September 29, 1999

JAMES C. HOUSEL 10/1/99
SUPERVISORY PATENT EXAMINER